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Further Clinical Delineation and Increased Morbidity in Males With Osteopathia Striata With Cranial Sclerosis: An X-Linked Disorder?

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Osteopathia striata with cranial sclerosis (OS-CS) is a bone dysplasia characterized by hypertelorism, macrocephaly, frontal bossing, broad nasal bridge, palate anomalies, hearing deficits, and mental retardation. The radiographic findings include cranial sclerosis, linear striations in the long bones and iliac wings, small poorly aerated sinuses, scoliosis, and increased bone density. The sensory deficits are disabling, but the condition generally is not life threatening.

We describe 4 brothers with the characteristics of OS-CS, 3 of whom have died from more serious complications of the disorder. The mother of these children, and her only daughter, have the mildest phenotype with the typical linear striations in the long bones and macrocephaly. OS-CS is thought to be autosomal dominant with complete penetrance and variable expressivity. Our observations could be consistent with X-linkage, since there is milder expression in the female relatives. In addition, we recognize absent fibulae, malrotation, and omphalocele as new manifestations as well as congenital heart disease. Am. J. Med. Genet. 70:159–165, 1997.

KEY WORDS: osteopathia striata; cranial sclerosis; omphalocele; bone dysplasia

INTRODUCTION

The term "osteopathia striata" refers to a radiographic finding of linear striations at the metaphyses of the long bones. It was initially described by Voorhoeve [1924]. It can occur as a benign isolated finding, or as part of a syndrome [Larregue et al., 1972; Whyte and Murphy, 1980]. Its association with cranial sclerosis was first noted by Hurt [1953]. Since then, over 35 cases have been reported [Gay et al., 1994]. Osteopathia striata with cranial sclerosis (OS-CS) is thought to be an autosomal dominant trait [Horan and Beighton, 1978] with complete penetrance and variable expressivity [Gay et al., 1994].

The characteristics of OS-CS are hypertelorism, macrocephaly, frontal bossing, broad nasal bridge, palate anomalies, hearing deficits, and mental retardation in some patients [Bass et al., 1980; Winter et al., 1980]. Skeletal abnormalities include CS, linear striations in the long bones and iliac wings, small poorly aerated sinuses, scoliosis, broad flat ribs, and increased bone density [Bloor, 1954; Paling et al., 1981]. The condition can be disabling due to hearing loss and cranial nerve palsies, but generally is not life-threatening. We report on 4 brothers with OS-CS, 3 of whom died of complications of their condition; the living brother has serious impairments. However, the sister and mother are only mildly affected. This pedigree may suggest X-linkage. We also recognize absent fibulae, malrotation, and omphalocele as new components of the disorder.

CLINICAL REPORT

Patient 1 (Male)

The propositus was born at 33 weeks of gestation to a then 26-year-old mother. The pregnancy was followed closely due to a history of 3 previous infant deaths associated with multiple congenital anomalies. The pedi-

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gree is given in Figure 1. Several level II ultrasound studies were done throughout the pregnancy and were normal until 24 weeks of gestation when a discrepancy was noted between head size and femur length. Polyhydramnios developed at 26 weeks, requiring 2–3 amniocenteses. A cleft palate was noted prenatally and fetal sex was 46,XY.

The infant was delivered by emergency cesarean section for increasing head size and enlargement of ventricles. Apgar scores were 5, 5, and 9, at 1, 5, and 10 minutes, respectively. The infant required resuscitation in the delivery room, and was noted to have macrocephaly. Birth weight was 2.5 kg (90th centile), length 47 cm (85th centile), and OFC 34 cm (>97th centile). The head was triangular in shape with a square forehead and frontal bossing (Fig. 2). A small upturned nose, wide nasal bridge, bow shaped mouth with downturned corners, and low-set ears were noted. There was a cleft of the hard palate and wide-spaced nipples. Fifth finger clinodactyly was noted bilaterally. His neonatal course was complicated by apnea requiring intubation and eventual tracheostomy, malrotation of the gut, and a ventricular-septal defect, patent ductus arteriosus, and a patent foramen ovale.

On follow-up exam at 5.5 years, the OFC was 56 cm (>98th centile). He had frontal bossing with bitemporal narrowing, occipital prominence, and a palpable ventriculoperitoneal (VP) shunt. He has epicanthal folds and hypertelorism. The ears are apparently low set, posteriorly angulated, small, and overfolded. There is a flat nasal bridge, fullness to the philtrum and upper lip, and micrognathia.

His muscular ventricular-septal defect closed spontaneously, but he required surgical repair of the intestinal malrotation, VP shunting for hydrocephalus and repair of cleft hard and soft palates, and treatment for a seizure disorder; partial agenesis of the corpus callosum was noted on a CT scan.

Skull radiographs show an unusual trapezoid-shaped skull with macrocephaly, CS, and narrowing of the supraorbital fissures (Fig. 3A,B). CT scan documented hydrocephalus, cortical atrophy, and a square shape of the skull (Fig. 3C). In addition, broad flat ribs, osteosclerosis, and mild thoracolumber gibbus with an unusual type of beaking of the L1 vertebral body were seen on chest and spine radiographs (Fig. 3D,E). Very faint vertical striations are present on a radiograph of the knees (Fig. 3F).

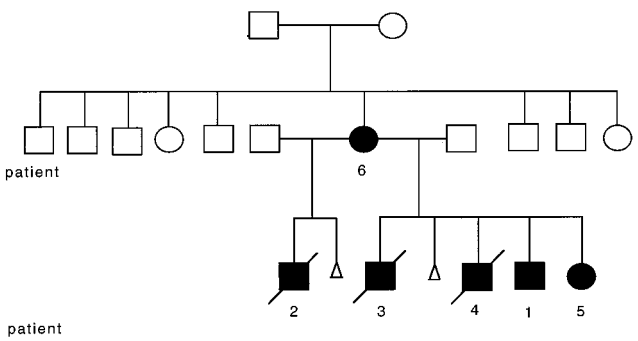

Fig. 1. Pedigree of the family. Affected members are solid symbols.

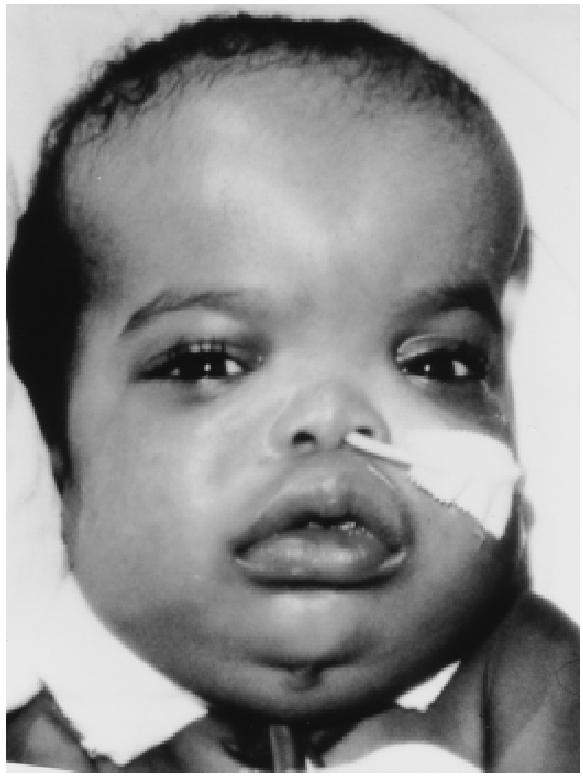

Fig. 2. Photo of patient 1 in infancy. Note bitemporal narrowness, macrocephaly, frontal bossing, hypertelorism, and epicanthal folds.

Patient 2 (Male)

The patient was the first born and the half sib (maternal) of patient 1. His gestation was complicated by oligohydramnios and mild preeclampsia. He was born by cesarean section due to failure to progress at 42 weeks of gestation with a weight of 4.8 kg (>97th centile), OFC 40 cm (>95th centile), and length 52 cm (75th centile). Multiple congenital anomalies included omphalocele, large fontanelle with wide sutures, frontal bossing, an abnormal left ear, webbed neck, wide-spaced nipples, second finger camptodactyly bilaterally, clubbed feet, and hypotonia. In addition, he had malrotation with gastric volvulus, right multicystic kidney, left nonfunctional kidney, seizures, atrial septal defect, ventriculoseptal defect, patent ductus arteriosus, and tricuspid insufficiency. The infant died of heart failure at 3 months. Chromosomes were normal 46,XY. No autopsy was performed.

Review of his radiographs showed generalized diffuse osteosclerosis and a bell-shaped thorax.

Patient 3 (Male)

The patient was the second born child and full sib of patient 1. Mother had preeclampsia. Results of a prenatal ultrasound study were normal. The infant was born at term by repeat cesarean section. His birth weight was 3.2 kg (50th centile), length 53 cm (90th centile), and macrocephaly was noted. He had a trapezoid shape of head with frontal and occipital bossing,

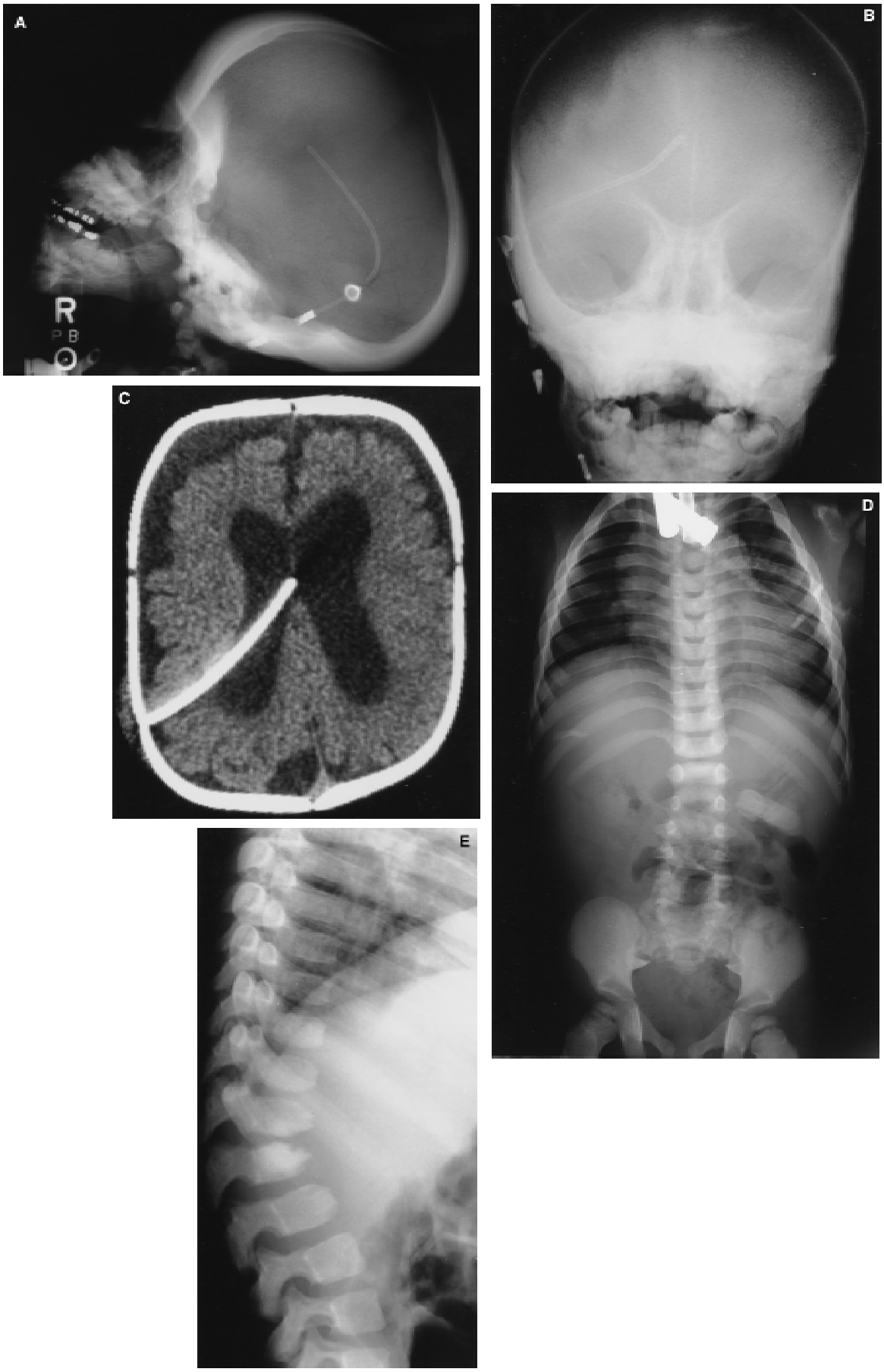

Fig. 3. Panel F and legend on overleaf.

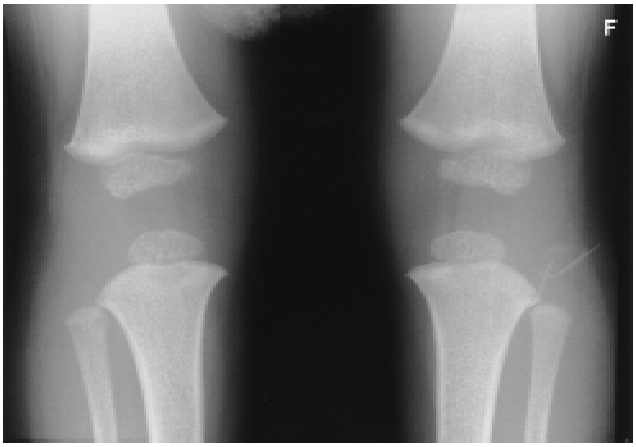

Fig. 3. Patient 1. Lateral **(A)** and frontal **(B)** skull radiographs show sclerosis and thickening of the calvaria which has a trapezoidal shape. The orbital fissures appear disproportionately small and the skull base is dense and thick. A ventricular shunt catheter extends from a right temporal craniotomy. **C:** An axial CT scan shows the square shape of the skull, dilated ventricles, and increased subarachnoid spaces consistent with external hydrocephalus and cerebral atrophy with a ventricular shunt in place. **D:** A frontal radiograph of the chest and abdomen shows broadened ribs. A tracheostomy tube is present. There is a mild sclerosis of the lower thoracic and first lumbar vertebrae. **E:** A lateral view of the thoracolumbar spine shows sharp angulation at the level of L-1. This vertebral body is small, sclerotic, and irregularly notched at the upper and lower anterior corners. **F:** Frontal views of both knees show subtle, linear, metaphyseal striations.

wide fontanelles, hypertelorism, apparently low-set ears, micrognathia, cleft palate, bifid uvula, bifid epiglottis, wide-spaced nipples, micropenis, undescended left testicle, hypoplastic maxilla, incomplete malrotation with left liver and right small bowel, and atrial and ventriculoseptal defects.

Radiographs showed dramatic CS (Fig. 4A), a trapezoid head shape, macrocephaly, absent fibulae, abnormal left seventh rib, osteosclerosis, and delayed knee ossification centers at birth (Fig. 4B). A CT scan at 15 months showed minimally increased ventricles and some cortical atrophy.

The infant died at 2.5 years of an aspiration after multiple hospital admissions for recurrent pneumonia. Chromosomes were normal 46,XY. No autopsy was performed.

Patient 4 (Male)

The patient was the third child and full sib of patients 1 and 3. Prenatally there was polyhydramnios and a history of poor prenatal care. The infant was born at term by repeat cesarean section with a weight of 3.4 kg (50th centile), length 49 cm (25th centile), and OFC 36.5 cm (90th centile). Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. He had a triangular-shaped head, hypertelorism, posteriorly angulated ears which were apparently low set and simple, bilateral cleft lip and palate, bifid uvula and epiglottis, broad thumbs, and clinodactyly of the first toe. Echocardiogram was normal; a malrotation was suspected. The infant died of aspiration at age 4 days. Autopsy was not performed, no chromosomes were obtained.

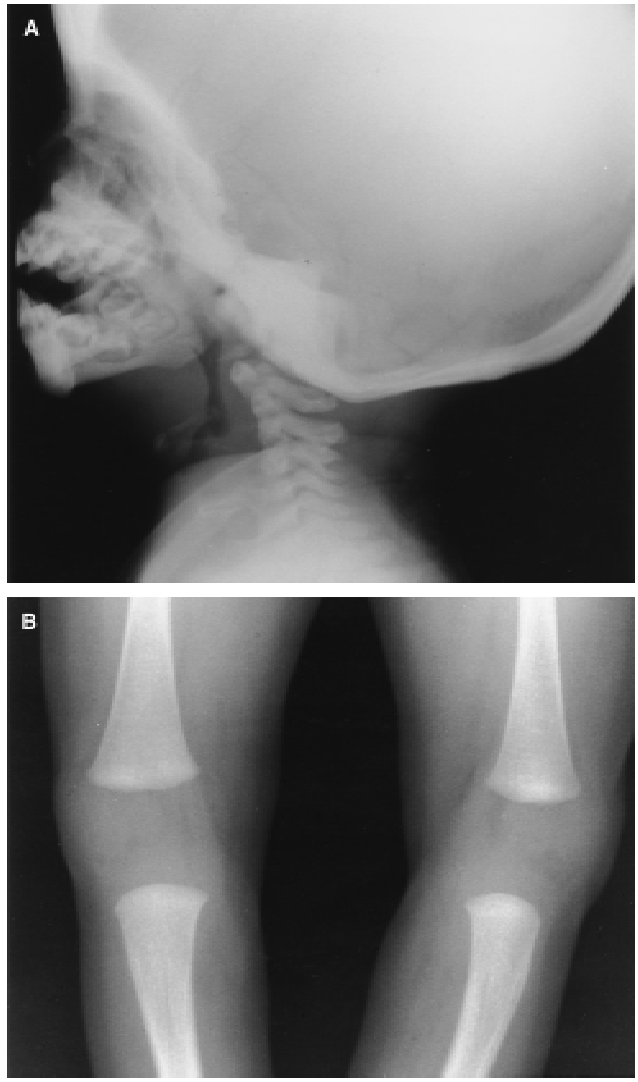

Fig. 4. Patient 3. **A:** A lateral view of the head and neck show cranial enlargement and dense sclerosis especially at the base and frontal regions. The mandible and maxilla are small with crowding of the teeth. A cervical kyphosis is present. **B:** Frontal view of both knees shows absent secondary ossification centers indicative of delayed maturation, with no evidence of striations. Both fibulae appear absent.

Skull radiographs demonstrated macrocephaly, trapezoid skull, CS, and mild osteosclerosis (Fig. 5).

Patient 5 (Female)

The patient is the fifth child and full sib of patients 1, 3, and 4. Prenatal history is unremarkable. The infant was born at term by repeat cesarean section with a weight of 3.27 kg (50th centile), a length of 48 cm (30th centile), and 3 teeth. Neonatally the infant had hyperbilirubinemia; at 4 months the infant was macrocephalic with an OFC of 43.8 cm (98th centile), length of 63.5 cm (80th centile), and weight of 6.8 kg (90th centile). At 10 months she was evaluated by genetic consultation and was noted to have frontal bossing and macrocephaly. Her OFC was 49.5 cm (>97th centile).

Fig. 5. Patient 4. A frontal radiograph shows the trapezoid shape of the skull and mild sclerosis of the orbits and petrous bones.

Radiographs at 10 months showed the characteristic trapezoid skull shape, macrocephaly, mild CS especially involving the petrous bones, and OS at the metaphyses of humeri, tibiae, femora, ankles, and at iliac crests (Fig. 6A–D).

Patient 6

The mother of these sibs has an OFC of 62.3 cm (>97th centile) and is 172.5 cm tall (25th centile). She had a history of a laryngeal web. Chromosomes are normal 46,XX. Radiographs showed CS, the trapezoid skull shape, macrocephaly, and OS of the long bones (Fig. 7).

Family History

The mother of these children has 8 normal sibs; none of their children are affected. She was born to a 28-year-old mother and a 32-year-old father.

DISCUSSION

We describe 6 individuals with OS-CS in one family. Three of 4 affected male children have died of complications from this disorder. The only living male child is severely impaired with hydrocephalus (requiring a VP shunt), a seizure disorder, and mental retardation. The mother of these children has the mildest phenotype with the typical linear striations in the long bones and macrocephaly. Her only daughter (patient 5) shares these milder findings. However, the male children (patients 1–4) have had serious complications with a variety of clinical findings (Table I) including macrocephaly with a triangular head shape, frontal bossing, a wide flat nasal bridge, hypertelorism, and less severe linear striations of the long bones. In addition, there are several variable features. Three of 4 affected boys had cleft palate, one also a cleft lip. Patients 1, 2, and 3 all had a congenital heart defect. Three of the 4 males also had a documented malrotation with an additional one suspected. Patient 2 had an omphalocele. Our experience suggests that males may have an increased morbidity and mortality associated with the more serious complications of OS-CS.

Malrotation has not been previously reported in this syndrome. In review of the literature, we were able to find a single case report with an omphalocele as in our case 2. The mother was mildly affected while her son had multiple anomalies [Currarino and Freidman, 1986]. He had several skeletal abnormalities including flexion deformities of the digits, a short fibula, and mild cervical kyphosis similar to our patients. Interestingly, the mother had a prior pregnancy resulting in a male child with an omphalocele, cleft palate, hypospadis, and enlargement of the head with biparietal bossing. On autopsy, histologic sections of the parietal bones showed "marked thickening of the inner and outer table with decreased bone marrow spaces." It is likely that this patient had the same condition as his sib and our patients.

At an early age, the radiographs of patients 1–4 all demonstrated osteosclerosis without OS. Patient 1 developed subtle striations; however, patients 2–4 died before the typical striations were seen. Interestingly, the mother had OS as did her daughter (at age 10 months). Our patients suggest that the striations may not appear in infancy, making the diagnosis difficult in the early years of life.

Congenital heart defects have been previously described in OS-CS and were noted in 3 of our 6 patients. Prior reports have described mild pulmonic stenosis [Currarino and Friedman, 1986], ventriculoseptal defects [Odrezin and Krasikov, 1993; Kornreich et al., 1998], atrial-septal defects [König et al., 1996], mitral valve insufficiency/stenosis [König et al., 1996], and primary AV block with left ventricular hypertrophy and a ventriculoseptal defect [Clementi et al., 1993].

While all the children were born to the same mother, there are 2 fathers. OS-CS is thought of as an autosomal dominant trait. In review of the other reported cases, the evidence for autosomal dominant vs. X-linked is not conclusive. There is only one reported case of male-to-male transmission supporting this mode of inheritance [Horan and Beighton, 1978]. The female index case and her paternal grandmother were affected. The patient's father and her paternal half-brother were reported to have the facial changes of the disorder but radiographs were not obtained. Other cases [Cortina et al., 1981; Currarino and Freidman, 1986; Nakamura et al., 1985; Horan and Beighton (kindred 1), 1978] all have affected women who had sons that were similarly or more severely affected. In a large 3-generation family [Winter et al., 1980], a mildly affected father had a more severely affected daughter who then had both an affected son and daughter. The son died on the 6th day of life. Recently a 4-generation

Fig. 6. Patient 5. Lateral **(A)** and frontal **(B)** skull radiographs show mild frontal bossing and a slightly trapezoid shape. The petrous bones are sclerotic but the rest of the skull is normal in thickness and bone density. Views of the left humerus **(C)** and both knees **(D)** show characteristic, longitudinal, linear, and metaphyseal striations.

kindred was described; in the maternal line there were 5 affected females and a single male [König et al., 1996]. The male had typical manifestations but also had Pierre Robin sequence, tracheomalacia, flexion contractures, short stature, and hypotonia.

OS-CS is 2.5 times more common in females [Gay et al., 1994]. Our observation is highly suggestive of X-linkage since the females are so mildly affected while the male children have severe morbidity and high mortality. The other cases discussed could also be consistent with X-linkage. Further work on the molecular level in our study and others will be needed to address genetic heterogeneity and confirm the inheritance pattern.

TABLE I. Summary of Clinical Features

Patient	2	3	4	1	5	6
Macrocephaly	+	+	+	+	+	+
Frontal bossing	+	+	+	+	+	+
Cleft palate	–	+	+	+	–	–
Hypertelorism	?	+	+	+	–	+
Congenital heart disease	+	+	–	+	–	–
Malrotation	+	+	+/–	+	–	–
CS	?	+	+	+	+	+
OS	–	–	–	+	+	+
Absent fibula	–	+	–	–	–	–
Hand abnormalities	+	–	+	+	–	–
Natal teeth	–	–	–	–	+	–
Laryngeal web	–	–	–	–	–	+

Fig. 7. Patient 6. A lateral skull radiograph shows dense sclerosis of all the bones of the skull including the facial bones. The maxilla and mandible are particularly thick and dense.

REFERENCES

Bass HN, Weiner JR, Goldman A, Smith LE, Sparkes RS, Crandall BF (1980): Osteopathia striata syndrome. Clin Pediatr 19:369–373.

Bloor DU (1954): A case of osteopathia striata. J Bone Joint Surg [Br] 36:261–265.

Clementi M, Bellato S, Rossetti A, Mammi I, Tenconi R (1993): Is visual field reduction a component manifestation of osteopathia striata with cranial sclerosis? Am J Med Genet 46:724–726.

Cortina H, Vallcanera A, Vidal J (1981): Familial osteopathia striata with cranial condensation. Pediatr Radiol 11:87–90.

Currarino G, Friedman JM (1986): Severe craniofacial sclerosis with multiple anomalies in a boy and his mother. Pediatr Radiol 16:441–447.

Gay BB Jr, Elsas LJ, Wyly JB, Pasquali M (1994): Osteopathia striata with cranial sclerosis. Pediatr Radiol 24:56–60.

Horan FT, Beighton PH (1978): Osteopathia striata with cranial sclerosis. An autosomal dominant entity. Clin Genet 13:201–206.

Hurt RL (1953): Osteopathia striata—Voorhoeve's disease: Report of a case presenting features of osteopathia striata and osteopetrosis. J Bone Joint Surg [Br] 35:89–92.

König R, Dukiet C, Dörries A, Zabel B, Fuchs S (1996): Osteopathia striata with cranial sclerosis: Variable expressivity in a four generation pedigree. Am J Med Genet 63:68–73.

Kornreich L, Grunebaum M, Ziv N, Shuper A, Minouni M (1988): Osteopathia striata, cranial sclerosis with cleft palate and facial nerve palsy. Eur J Pediatr 147:101–103.

Larregue M, Maroteaux J, Michel Y, Faure C (1972): Osteopathia striata: Radiological manifestations of focal dermal hypoplasia. Ann Radiol (Paris) 15:287–295.

Nakamura T, Yokomizo Y, Kanda S, Harada T, Naruse T (1985): Osteopathia striata with cranial sclerosis affecting three family members. Skeletal Radiol 14:267–269.

Odrezin GT, Krasikov N (1993): CT of the temporal bone in a patient with osteopathia striata and cranial sclerosis. AJNR 14:72–75.

Paling MR, Hyde I, Dennis NR (1981): Osteopathia striata with sclerosis and thickening of the skull. Br J Radiol 54:344–348.

Voorhoeve N (1924): L'image radiologique non encore déscrite d'une anomalie du squelette. Acta Radiol 3:407–427.

Whyte MP, Murphy WA (1980): Osteopathia striata associated with familial dermopathy and white forelock: Evidence for postnatal development of osteopathia striata. Am J Med Genet 5:227–234.

Winter RM, Crawfurd MD, Meire HB, Mitchell N (1980): Osteopathia striata with cranial sclerosis: Highly variable expression within a family including cleft palate in two neonatal cases. Clin Genet 18:462–474.